REMARKS

Support for amendment of claims

In amending the claims, applicants have taken care to avoid the introduction of new matter and used only language or disclosure from the specification, in accordance with MPEP 608.01(o). Support for the subject matter of the amended claim is as follows.

Support for the claim terminology "single chain polypeptide" is found at page 7, lines 22-23 of the specification, wherein it is stated that "[s]uch chimeric polypeptides, also referred to herein as 'single chain' molecules."

Support for the claim terminology "an amino acid sequence spacer linked to both the virus coat polypeptide sequence and viral receptor polypeptide sequence and positioned therebetween to form a single chain polypeptide" is easily seen in Figure 1 and discussed consistently through the entire specification.

Support for the claim terminology "a viral receptor polypeptide sequence having a bonding affinity for the virus coat polypeptide sequence" is found at page 19, lines 11.

Support for the claim terminology "an intramolecular interacting complex" is found at page 35, lines 14-15 and page 37, lines 12-13.

Support for claim 73 is found at page 3, lines 21-22, page 4, lines 9-10 and page 7, lines 16-17.

Supplemental IDS

Applicants submitted Supplemental Information Disclosure Statements on August 26, 2002 and October 24, 2002 and although the Office make reference to the IDS form 1449 being attached to the instant Office Action, the applicants could not locate such documents. As such, applicants are requesting that the Office forward a second copy of both Supplemental IDS forms sent on August 26, 2002 (paper 16) and October 24, 2002 (paper 17).

Rejections of Claims and Traversal Thereof

In the October 22, 2002 Office Action,

claims 1-3, 6-16 and 24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chackerian, et al. (Proceedings of the National Academy of Sciences, March 1999) and U.S. Patent No. 5,843,454 (DeVico, et al., hereinafter DeVico '454).

The rejection of claims 1-3, 6-16 and 24 is hereby traversed, and reconsideration of the patentability of amended claims 1-3, 6-16 and 24 is requested, in light of the ensuing remarks.

Rejection under 35 U.S.C. §103(a)

Claims 1-3, 6-16 and 24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chackerian, et al. and DeVico '454. Applicants submit that the combination of the two cited references does not in any way render applicants' claimed invention *prima facie* obvious.

The present invention relates to a single chain chimeric polypeptide that includes a virus coat polypeptide sequence, a viral receptor polypeptide sequence that has a bonding affinity for the virus coat polypeptide sequence, and an amino acid sequence spacer having a first end linked to the virus coat polypeptide sequence and the opposite end linked to the viral receptor polypeptide sequence to form a single chain polypeptide, wherein the amino acid spacer consists of a sufficient length of amino acid residues to allow the single chain chimeric polypeptide to fold thereby permitting the virus coat polypeptide sequence and the viral receptor polypeptide sequence to form an intramolecular interacting complex.

Chackerian, et al. relates to a method for disguising self-proteins for recognition as foreign antigens. Chackerian, et al. suggests that antigen arrangement may be a major determinant in inducing B cell responsiveness to self proteins and discusses the importance of an ordered array of the antigen in the whole viron. The reference describes inserting a native self protein as part of a highly organized array of an assembled viral capsomer that can induce production of autoantibodies against the native self-protein. Chackerian, et al. accomplished this purpose by

inserting a self-peptide, which was an extracellular (EC) loop of the mouse C-C chemokine receptor CCR5, into the viral capsid (L1) protein from bovine papillomavirus type 1. The bovine papillomavirus has the intrinsic capacity to self-assemble into virus like particles that induce high levels of neutralizing antibodies. The chimeras of Chackerian, et al. were constructed by inserting the mCCR5 within the sequence for L1, that being the mCCR5 protein was flanked on both sides by sequences of the L1 protein. Specifically, as stated at page 2372 in column 2, the mCCR5 replaced amino acids 130-136, 275-285 or 344-350 of the L1 sequence.

Initially, it should be noted that there is no teaching or suggestion that the self-protein and the viral capsid protein have any affinity for binding to each other when they are combined into the chimeric polypeptide. Thus, they are certainly not a receptor/ligand pair. Further, there is no teaching or suggestion to separate the two proteins by an amino acid spacer that is of a sufficient length of amino acid residues to allow the polypeptide to fold and form an intermolecular interacting complex between the two different proteins.

Instead, antibody production, relative to the unassembled structure, was in response to the mCCR5 inserted in an orderly fashion in the viral capsid protein. As stated at page 2374, at the bottom of column 2, the self-proteins were inserted in areas of the viral capsid protein that would not interrupt the assembly process but would present the self-antigens as specific reactive epitopes. Thus, both applicants and the Office agree that the chimeric polypeptide described by Chackerian, et al. has the ability to reassemble into the viral capsid tertiary structure.

The Office recognizes that Chackerian, et al. does not teach a chimera of a retrovirus coat protein and a viral receptor protein linked by spacer amino acids. To overcome the deficiencies of the Chackerian, et al. reference, the Office introduced the DeVico '454 reference because according to the Office, "DeVico, et al. disclose in both patents a CD4-gp120 complex that have been covalently linked using a reactive spacer molecule." It is noted by applicants that the Office also recognizes that the DeVico '454 reference, like the Chackerian, et al. reference, "does not teach an amino acid spacer in the production of the antigenic complex."

However, the Office contends that:

> "it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex. . . . One of ordinary skill in the art would have the high expectation of success when expressing the complex as a single polypeptide. The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the chimera."

Applicants vigorously disagree. Clearly neither reference teaches or suggests going in the direction of applicants' claimed invention, which uses an amino acid spacer positioned between the virus coat protein and the viral receptor protein to allow the single chain polypeptide to fold and form an intramolecular interacting complex.

What is the asserted motivation put forth in either reference to insert amino acid sequence between the different peptides of either reference for the purpose to enhance folding and/or complex forming? Clearly there is no motivation and the Office has not provided any to date. As discussed above, the Chackerian, et al. reference described that the L1-CCR5 chimera eluted in a fraction indicating an assembled particulate structure. The reference further states that examination of the chimera particle by electron microscopy revealed many particles that were smaller than wild type but morphologically the L1-CCR5 chimeric particles resembled polyomavirus 12 IOSCA shells. Clearly the Office agrees with the above discussion because it is expressly stated in the Office Action of October 22, 2002 that "[t]he reference makes no discussion of using spacer amino acid yet the chimera is able to form the requisite tertiary structure indicating that a spacer is not required for the structure." Thus, the Chackerian, at al. provides no motivation to go in the direction of applicants' claimed invention, because in fact the capsid reassembles properly.

Likewise, after thorough review of DeVico '454, applicants cannot find any motivation to form a single chain polypeptide that includes the virus coat polypeptide sequence and the viral receptor polypeptide separated by an amino acid spacer. Instead, DeVico '454 stresses the importance of covalently bonding the gp120 protein directly to the CD4 receptor protein to ensure that the two soluble proteins are not separated when in use. DeVico '454 discusses numerous times the instability of the prior art complexes, and the fact that unless the two proteins were crosslinked

the two proteins would separate and antibodies would not be produced for the cryptic epitope but instead one of the uncomplexed proteins. For example, as discussed at column 2, lines 42-45 "Immunization with soluble CD4 and recombinant gp120, complexed by their natural affinity but not covalently bonded, resulted in the production of anti CD4 antibodies." It is further stated in column 2, that "the complexes used in these studies were unstable and comprised noncovalently bound gp120 and CD4." To overcome the shortcomings of the discussed prior art, DeVico '454, as stated at column 4, lines 46-51, "used a covalently linked gp120-CD4 complex as an immunogen. gp120 was covalently coupled to soluble recombinant CD4 using bivalent cross-linking agents to ensure that the integrity of the complexes was maintained during any manipulations."

Considering the importance of the covalent bond between the gp120 and CD4 proteins and the discussion that a noncovalently bonded complex was not effective, applicants submit that DeVico '454 teaches away from applicants' claimed single chain polypeptides. Clearly, one reading DeVico '454 would not be provided with any incentive to insert an amino acid spacer between the virus coat protein and the viral receptor protein. Nor is there any indication that such a complex would be effective, especially because applicants' formed complex is maintained by bonding affinity. The Court in *In re Gurley*, 31 USPQ 2d 1131 (Fed. Cir. 1994) addressed the issue of a cited reference that teaches away from a claimed invention and stated:

> "[I]n general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant."

DeVico '454 teaches that forming a noncovalently bonded complex has several inherent problems such as the two soluble proteins becoming uncomplexed and this was the impetus for DeVico '454 to form a covalent bond between the gp120 and the CD4 by crosslinking the two soluble proteins together. However, applicants have shown that if the amino acid sequence spacer is of sufficient length, a stable complex can form and this fact is proven in the results of the examples set forth in the present application. Specifically, in Example 3, the single chain polypeptides of the present invention were tested using monoclonal antibodies that previously

showed that a properly folded gp120-CD4 was formed. Likewise, in Example 4, it was shown that the single chain gp120-CD4 complex bound to CCR5-expressing cells. The single chain polypeptides of the present invention would not have bound to the CCR5-expressing cells unless the properly folded gp20-CD4 complex had formed.

In order to determine obviousness, it is incumbent upon the Office to view the invention as a whole. *In re Wesslau*, 174 U.S.P.Q. 393 (CCPA 1965). Also, the Office must consider the inventions of the cited references in their entireties. Certain individual features from the references may not be chosen and merely lumped together as a mosaic in an attempt to meet the features of the rejected claims. This legal concept is important for the Office to remember when attempting to combine prior art that teach entirely different chimeras or complexes, especially because neither reference describes or recognizes the importance of the amino acid spacer. As such, even if the two references were combinable, which they are not, they do not describe, teach or suggest all the claim limitations recited in applicants' claimed invention.

Further, applicants submit that the Office failed to give weight to the advantages and benefits of the present invention as part of the "invention as a whole" and cited references that do not disclose or teach such advantages or benefits. Applicants at page 14, lines 7-9 in the specification posits that:

> "the spacer allows the movement or flexibility between receptor and virus coat polypeptide sequences to form an interacting complex."

Obviously, neither the combination of cited references nor the individual references recognize the benefits of the present invention. Instead DeVico '454 goes the extra step to ensure that the gp120 protein is covalently bonded to the CD4 protein by crosslinking the complex. Chackerian, et al. is not even concerned with an interacting complex because the ordered array of antigen interdispersed in the viral capsid sequence provides the production of antibodies for the self protein and theVP1 capsid assembles without any further need of an amino acid spacer.

According to the Office;

> "The chimera as taught by Chackerian, et al. requires the single process step utilizing affinity purification after the expression of the chimer in an insect cell. One having ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to achieve conformation complex as taught by DeVico, et al. which would have the advantage of requiring less process steps in order to achieve the same function. The prior art requires purifying the CD4 and the gp120 proteins separately allowing them to interact and then chemically crosslinking followed by the removal of the excess cross linker."

Clearly the DeVico '454 reference gives no indication that a shortcut would improve the described covalently bonded complex. DeVico '454 requires crosslinking because as stated numerous times in the reference, covalent bonding of the gp120 protein to the CD4 by crosslinking is very important to maintain the integrity of the complex. There is no suggestion to produce a complex that is not covalently bonded because of the cited problems with complexes that were not covalently bonded. Applicants suggest that if the DeVico '454 crosslinked complexes were made according to the methods described by Chackerian, et al. then the DeVico '454 complexes would no longer be chemically crosslinked and thus would not function as intended. According to the court in *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.

Applicants argue that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination and suggesting the desirability of the combination Applicants respectfully submit that the Office's statement that the claimed invention would be obvious to one having ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. According to the Board in *Ex parte Obukowicz*, 27 U.S.P.Q. 2d 1063, 1065 (B.P.A.I. 1992):

> "In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art....The examiner can satisfy this burden only by showing some **objective** (emphasis added) teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teaching of the references."

See also *Ex parte Humphreys*, 24 USPQ 2D 1255, 1262 (B.P.A.I. 1992) where the Board addressed this very issue and determined the Office was wrong in rejecting the claims for obviousness because the examiner's rejection was not **specific** as to how one of ordinary skill in the art would have found it obvious to combine the references. Furthermore, they noted the examiner had not explained with any **specificity what areas of the references would suggest the combination**.

This is the circumstance here. The Office has not identified any objective or specific teachings or suggestions in the cited references that would motivate one skilled in the art to combine the references. Neither reference uses an amino acid spacer, Chackerian, et al. does not teach or suggest a receptor/ligand pair but instead inserting self proteins in a viral capsid protein in an acceptable order to trick the body into believing that the self protein is in fact a foreign antigen and DeVico '454 teaches the importance of chemically crosslinking two soluble proteins into a covalently bonded complex. Surely one skilled in the art would never consider combining the two references and uncrosslink the DeVico '454 complex and put the two soluble proteins into the Chackerian, et al. arrangement and then somehow determine that an amino acid sequence of a sufficient length positioned between the two proteins would allow for a stable complex, absent a reading of applicants' present application. Thus, the Office seems to be merely reinterpreting the prior art in light of applicants' disclosure, in order to reconstruct applicants' claimed invention, but without any instructional or motivating basis in the references themselves. Such approach is improper and legally insufficient to establish any *prima facie* case of obviousness.

In light of the above discussion and the fact that the Office has not met its burden of establishing a *prima facie* case of obviousness, applicant requests that the rejection of claims 1-3, 6-11, 13-16 and 24, on the basis of obviousness, be withdrawn.

Conclusion

Applicants have satisfied all the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that

Examiner Winkler reconsider the patentability of claims 1-3, 6-11, 13-16 and 24 in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Winkler is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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